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British Society for the History of Pharmacy
Q House, Troon Way Business Centre, Humberstone Lane,
Thurmaston, LEICESTER LE4 9HA

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British Society for the History of Pharmacy

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The British Society for the History of Pharmacy was formed in 1967 under the aegis of the Pharmaceutical Society of Great Britain, having originated from its History of Pharmacy Committee.

BSHP seeks to act as a focus for the development of all areas of the history of Pharmacy, from the works of the ancient apothecary to today's ever changing role of the community, hospital, wholesale or industrial pharmacist. Membership is open to all interested in the aims of BSHP.

Aims

Promotion of historical studies related to pharmacy.
Advancement of knowledge and propagation of understanding of the history of pharmacy.
Publication of the research work of pharmaceutical historians.
Preservation of pharmaceutical artefacts and historic pharmacies.
Support for the work of relevant museums and offering advice on establishment of other pharmaceutical exhibits and on the preservation of pharmacies.
Co-operation with related professions and local historians on medico-pharmaceutical topics of mutual interest.

Pharmaceutical Historian

The *Pharmaceutical Historian* has been published since 1967, at first intermittently, but on a regular quarterly basis from 1972. Issues generally comprise 16 or 20 pages and cover.

An **index** for the years 1967-1995 was published in 1998, for 1996-2000 in 2000, for 2001-2005 in December 2005, for 2006-2010 in December 2010 and 2011-2015 in December 2015. They can be viewed on the website.

Papers, short communications and letters in English on any aspect of the history of pharmacy are welcome and should be sent to the address above or by email to *editor@bshp.org*

Any illustrations are converted to monochrome for printing. Further details of requirements can be found

Membership

Membership costs £20.00 per annum and includes:

Four issues of the *Pharmaceutical Historian.*

Regular meetings, with guest speakers, usually in November, February and May.

Visits to places of historic interest, museums, collections, botanical gardens, etc.

Annual Conference, usually in March/April.

Free use of the Royal Pharmaceutical Society of Great Britain's library facilities for research.

Help in historical research and with the identification of artefacts.

Affiliation to the International Society for the History of Pharmacy (ISHP).

Affiliation to the British Society for the History of Medicine (BSHM).

Application forms are available from the Honorary Secretary at the address above or on *www.bshp.org*

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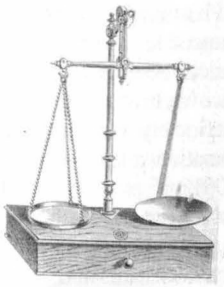

PHARMACEUTICAL HISTORIAN

Editor: Ainley Wade, BPharm, MPhil, FRPharmS
Q House, Troon Way Business Centre, Humberstone Lane,
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www.bshp.org

Contents

Diary

Please note the new addresses for the meetings.

Wednesday 6 July 2016
Visit to The Linnean Society Library, Burlington House, Piccadilly, London W1J 0BF. 2.00 pm. Application forms enclosed with this issue.

Monday 10 October 2016
'Expedition medicine' by Dr Henry Guly, retired consultant in emergency medicine, at 5:30pm, with refreshments from 5:00pm. UCL School of Pharmacy, 29-39 Brunswick Square, London WC1N 1AX
Nearest tube: Russell Square

Monday 7 November 2016
Joint meeting with Bradford School of Pharmacy. Further details to follow.

BSHP has its own **Facebook** page. 'Like' us to share information on events, news items, resources, research and other pharmacy history topics from BSHP and related organisations.

One pharmacy world-view 1963-74 using perspectives of Schütz

Malcolm E Brown MPhil, PhD, MRPharmS
Beccles, Suffolk

The Oxford Dictionary defines history as 'the study of past events, particularly in human affairs'. Countless historians, philosophers and others have considered what history is. I have studied the perspective of the social scientist **Alfred Schütz** (1899-1959) and find it fruitful. Briefly, the 'life world' of 'us' and 'them' has four perspectives, numbered in order of increasing distance.[1]

Firstly, the individual and others face-to-face ('consociates') during the same time and space is the most immediate, vivid and accurate. Only with consociates is it possible to hear the tone of voice, watch body language, look into their eyes and ask what something *means*.[2,3,4] The **second** is others only known indirectly at the same time. Increasing anonymity can be mapped, such as patients in general, the General Pharmaceutical Council or its artefacts such as a register. The **third** is the world of the predecessors. They may speak to us through their vestiges such as audio or video recordings, publications, traditions or artefacts. Vestiges include prescription books, symbols of professional body or medicines such as an ancient pot containing eye ointment that can be analysed. Myths are ancient vestiges, potentially garbled and ambiguous that, to a predecessor, *may* have been eye-witness experience. The 'Recipe' symbol in Figure 1 may be an invocation to the planet (god) Jupiter for the medicine to work; around 1963, a pharmaceutics lecturer (Dr Geoff Booth) shared that muted origin. The large status difference between respected lecturer and me (a student) contributed towards my still remembering the myth in 2016 – not because Haggard (1929) had documented it in *Devils, Drugs, and Doctors: The Story of the Science of Healing from Medicine-Man to Doctor*. The **fourth** perspective is our successors. Our relationship to them is the reciprocal of

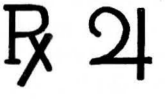

Figure 1. 'Recipe' (Take thou) instruction, and astrological symbol for Jupiter.

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that to our antecedents. We may send our successors a message, such as in the *Pharmaceutical Historian,* but only one way: towards the future. A two-way dialogue is impossible. To them, we are history.Arguably, the richest, most 'certain' type of history is that recounted by an individual who had face-to-face contact with a situation, the *grain* of lived reality.[5] Put differently, you are an *eye-witness*;[6] you remember an earlier you. There is a narrow window when memories are old enough to be deemed (modern) history yet that individual has survived long enough to report an eye-witness account, retains inclination and mental capacity, the surrounding culture is free enough to permit reporting[7] and so on.

In this article, this retired pharmacist, born in Coventry in 1945,[8,9,10,11] remembers and records lived personal experience as a pharmacy student, and early practice from about 1963 to 1974. I also comment on connection with events or trends that affect whole groups or societies that all of **Schütz**'s perspectives except his third (ancestors) may read about in history books. It lacks the forensic accuracy of the ethnographic field notes on community pharmacy recorded decades later.[12,13]

Two aspects struck me while writing this article. Firstly, and predictably, there is nostalgia: the rosy glow of 'the good old days" when medicines were just labelled 'The Tablets' and so on, the identity of the drug being withheld, and, using **Schütz**' s second perspective, more respect was afforded to the institution of medicine and its authority figures (such as practitioners). Second, on probing for details, most memories are of extreme events. That chimes with the newspaper headline writers' maxim, 'If it bleeds, let it lead'.

Student

Student days were not at university. After three science Advanced levels I attended Bradford Institute of Technology in 1963. When attending for interview in 1962, entrance was through the dark dingy technical college, 'the great and the good" of Yorkshire, such as Lord Mayors, looking down from begrimed oil portraits on walls.[14] Those worthies (from **Schütz**'s third perspective) humbled me and may have subdued my behaviour as applicant. That institute was one of ten colleges of advanced technology (CATs), created in 1956; while applying in 1962, I was aware of that raised profile[15] (*almost* as good as universities, using **Schütz**'s second perspective). All CATs later became universities; five CATs taught pharmacy.[16] I eventually received a Pharmaceutical Chemist Qualifying Diploma (PhC). I failed some final examinations. Had I passed them all first time, I would have received a Bradford BPharm degree. Before the 1960s, only about 2% of Britons in their early twenties graduated. During the 1960s that portion increased to about 6%. Today it is about 50%.[17] However, what it means for prestige to be a graduate differs today from, say, the 1950s: today graduate status is less prestigious. If prestige is connected with rarity, the mischievous might argue that, if graduates became a majority group, their status would fall below that of non-graduates.

The examining body was the Pharmaceutical Society. Even while studying for the Advanced levels universities set for entrance, the Pharmaceutical Society impressed me by having the power to set its own examinations that it would accept, instead.[18,19] That Society, then, had both regulatory and professional association roles. It loomed in student lives; it registered 100% of pharmacists. In 2015, only about 56% of pharmacists (i.e. registered with the General Pharmaceutical Council) were members of the Royal Pharmaceutical Society.[20] Its status in my eyes and, I suspect, those of government, patients and non-member pharmacists, has diminished.

One strategy to increase it is the recently-introduced faculty structure: certain members, after assessment, receive extra credentials. Eventually, faculty membership may become essential for top pharmaceutical positions, just as being a member of a medical royal college is required for certain NHS medical consultant positions.

Bradford CAT's 1963 student intake was about 90; it only included about 10 females (11%):[21] a small minority. Females comprised 59% of those first registering as pharmacists in Britain in 2011.[22] Females comprised 53% of new first-year MPharm students (n= 146) at Bradford in 2015.[23] Literature on feminisation of occupations and its implications is substantial, but sparse within pharmacy.[24,25,26,27] My pre-registration pharmacy student days were when the female emancipation movement was in its infancy; today a substantial literature exists that re-writes history from a feminist perspective. My lived (male) experience (1963-2016), using Schütz's first and second perspectives, feels turbulent.

In my 1963 intake at Bradford, students 'of colour' were about 4 (4%): a small minority;[28] 69% of those first registering as pharmacists in Britain in 2011 were from 'a black or minority ethnic background'. New first-year MPharm students at Bradford in 2015 comprised 12% 'African', 5% 'Arab', 8% 'Bangladeshi', 5% 'Chinese', 8% 'Indian' and 49% 'Pakistani' (totalling 87%: a large majority). The remainder were 6% 'other' and 7% 'unknown'.[30]

More pharmaceutically, only my student cohort was taught and examined in both apothecary (and Imperial) and metric units;[31] I was in the last year that was taught both units. The units to measure a drug were on a cusp. A drug changed from something measured in, for example, minims to mL.[32] Everybody's hands-on practical experience and observation of the size and amount of substance in a drop, and the simple intellectual (linguistic) connection that a drop was (about) a minim, vanished. From the perspective of the philosopher historian Michel Foucault (1926-84) that would not be a trivial matter: it illustrates how the very architecture of our world shifts and changes.[33,34] I lived though that change but, then, appreciated nothing of its philosophical ramifications.

In pharmaceutics, ingredients were unstated; calculating used logarithms; much extemporaneous dispensing from ground-glass-stoppered bottles sporting Latin names occurred and the demonstrator poured away any

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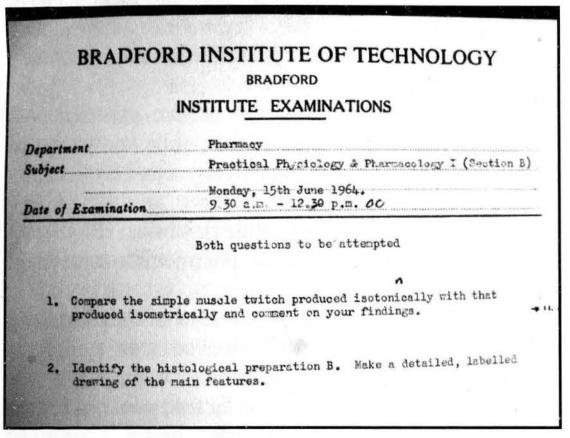
unlabelled preparation being compounded even if that had taken hours. Glycerin pessaries were 'tested' by tossing at the ceiling to check that they stuck, despite exhortations to avoid such tossing. Muscle twitches from many pithed frogs were traced on paper rotating on smoked drums (kymographs), and subsequently fixed with an alcoholic solution of shellac and colophony resin or other varnishing (solvent) solution.[35] Figure 2 reproduces an examination paper.



BRADFORD INSTITUTE OF TECHNOLOGY
BRADFORD
INSTITUTE EXAMINATIONS

Department: Pharmacy
Subject: Practical Physiology & Pharmacology I (Section B)
Date of Examination: Monday, 15th June 1964. 9.30 a.m. - 12.30 p.m. OC

Both questions to be attempted

1. Compare the simple muscle twitch produced isotonically with that produced isometrically and comment on your findings.

2. Identify the histological preparation B. Make a detailed, labelled drawing of the main features.

Figure 2. Examination paper, practical physiology and pharmacology, 1964.

Such study helped to emphasise respect for accurate observation and ingrain the scientific method. Subsequently, such study was most helpful to those undertaking scientific research in industry or academia but less relevant to the majority who would work in 'chemist shops'. At least one chemistry practical examination spanned six hours.[36] Examinees were accompanied to lavatories to ensure that they did not talk to each other.

My favourite subject was pharmacognosy, a name that feels antiquated to modern Western ears. It had few academic staff and most students thought it was irrelevant. However, I loved staining and looking at botanical tissues microscopically, identifying them and thinking about their countries of origin, such as Zanzibar and Penang for cloves: poetical-sounding far-flung territories. I loved to imagine alchemists and apothecaries manipulating those ingredients centuries before; my love of pharmaceutical history was born. As part of an examination we had to identify ten specimens, only seen fleetingly, lined up on a bench. Examination marking was 'negative': a correct answer gained a mark but an incorrect answer lost a mark. Guessing was imprudent: a sound tactic in pharmacy. To aid recognition, I stuck samples of each on sheets of cardboard by my bedside. Figure 3 portrays one such sheet. Figures 4 illustrates individual specimens about fifty years later after storage in seven successive lofts.

Most specimens remain fixed and identifiable although a detritus of broken bottles and assorted beetles litters the

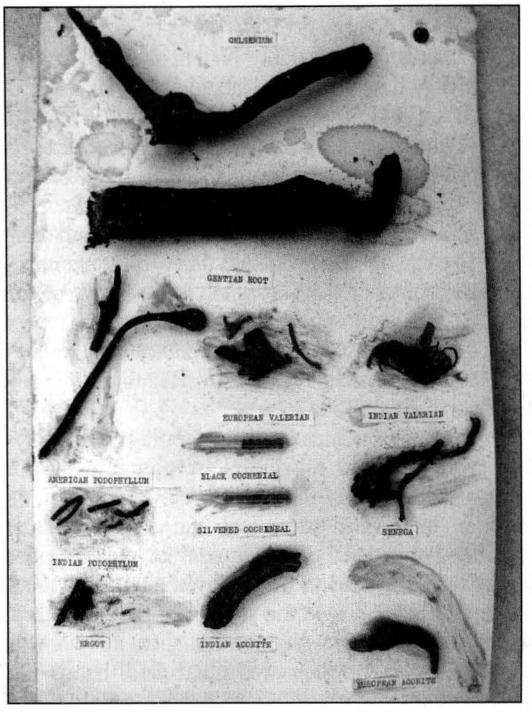


Figure 3. Sheet of pharmacognostical specimens.

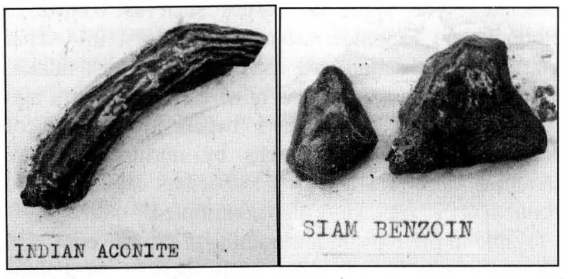


Figure 4. Individual specimens: Indian aconite, Siam benzoin.

bottom of the box. *Copydex* adhesive and cardboard (lignin) had yellowed and the cardboard (cellulose fibres) had weakened these amateurish exhibits.[37] Pharmacy studies had excluded conservation of museum artefacts.

"Don't taste the bisected *Nux vomica* bean," the demonstrator said. Most students tasted. Half a century later, I still remember the searing sharpness (strychnine) slashing my tongue.

I still remember 'the stack' in the College library. Pharmacy researchers, during literature searches, trawled there. Today such a stack would seem almost a museum relic. Had I been told, then, that I would be able to access 'all' published global research knowledge by stroking a finger on a small inexpensive hand-held wireless telephone and that most citizens of the planet carried such a device, I would have dismissed it as science fiction or even magic.[38]

Hospital

My pre-registration year was in Coventry hospitals, mainly at Whitley, then also known as the 'fever (infectious diseases) hospital'. Built in 1935, it replaced the isolation hospital built in 1874.

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My clearest memory is of a smell: ether soap. I inhaled it for hours, its pungent odour having a hint of lavender (volatile ingredients included about 0.2% lavender oil, 34% ethanol and 50% ether). I compounded that with *Milton* (about 1% available chlorine) and generic scouring powder so dusty that some smaller airborne particles must have lodged deep within the lungs. That cocktail plus elbow grease kept a pharmacy porcelain trough sparkling white. To clean it was my duty, as the lowliest member of staff; I remember the friction as the gritty sludge cut into stains. Risk of explosion did not occur to me. This was before the 'Health and Safety at Work Act' or 'Control of Substances Hazardous to Health Regulations'; other illustrations of risks follow later.

For example, I remember the slapping and slurping when I mixed five kilograms of glutinous creams, ointments and pastes directly on the bench top. My favourite ingredient was coal tar. One consultant dermatologist insisted on crude coal tar collected from the gas works instead of the wishy-washy 2% aqueous solution. Sulphur dusted the surface of the tar. I deeply inhaled the aroma for tar was not then known to be carcinogenic. The beaker was unlabelled, hands were regularly without gloves.

With evangelical zeal, we labelled multi-ingredient externals with approved names such as 0.00625% fluocinolone acetonide instead of *Synalar* 1 in 4. That caused consternation and merriment amongst nurses. Generic names are old hat now. But forty years ago hospital pharmacist pioneers began the process of fabricating novel stylish hats by nurturing generic labelling and prescribing.[40] Politicians attempting to reduce NHS expenditure also contributed.

While in pre-registration training at the Coventry and Warwickshire Hospital, the only person prestigious enough to dare visit wards and attempt to influence prescribing, such as annotating charts with generic names, was the Group Chief Pharmacist. Then, ward sisters, if pharmacy staff upset them, would order those interlopers off wards. They should return to where they belonged: the other side of the dispensing hole-in-the-wall, filling ward boxes in the basement or trolleys clinking with scalding-hot bottles of phenolic disinfectant. But those intrepid explorers persisted in venturing out. I attended a presentation from an American hospital pharmacist around 1970 about the value of the novel approach of 'ward pharmacy'. Ward, clinical and prescribing pharmacists followed. Today, prescribing pharmacists, PharmDs and pharmacist consultants flourish. A clinical role is the 'default' expectation.

My most momentous memory occurred on wards during a 'holiday' job before my pre-registration year started. I accompanied a pharmacist as a porter, staggering to collect a recalled batch of glass bottles containing intravenous fluids. Some injections when held up to the light were hazy with microbial contamination. They were quarantined and returned to *Evans* at Liverpool.

In 1972, as a hospital pharmacist in Yorkshire, I learned that at *Evans Medical's* factory an autoclave gauge[42] that always showed zero had been assumed to be faulty and so was ignored because, when kicked, a drain valve gurgled a loud raspberry noise. Another recall and six deaths resulted. My portering was before the Medicines Act, *Orange Guide to good pharmaceutical manufacturing practice*[43] or EU requirement for 'Qualified Persons (QPs)'; I am unaware that QPs have ever been mentioned in the *Pharmaceutical Historian.* This article will return to pharmaceutical quality assurance and my career.

Even before registration, my private experience of witnessing hazy injections and the public knowledge of death and subsequent media frenzy combined in my mind. Sociologically, such mixing of the private (generally unreported) and public (historical record) is a characteristic of a career; all pharmacists have it in abundance.

Registration, gaining the *imprimatur* of the examining body, was a big day and I swelled with pride. On registering, I remained in hospital pharmacy: this was quirky behaviour because it was then so poorly paid. On applying for a post around Manchester I received fourteen job offers. I choose Stepping Hill Hospital of Stockport and Buxton Hospital Management Committee.

Sometimes I was out-posted to the grandly-domed Royal Devonshire Hospital at Buxton. Its pharmacy occupied a converted stable; the split stable door remained. We locked the bottom half to exclude non-pharmacy staff. To treat arthritis, we issued gargantuan quantities of *Myocrisin* Injection [sodium aurothiomalate]. I was impressed that sodium *auro*thiomalate contained gold, reflected in its price. Today, gold is inexpensive compared with the bioengineered medicines that I could not foresee during 1963-74.

At Stockport, I mainly produced sterile products and helped commission a new sterile area. It flaunted wall-to-ceiling windows so passers-by could see inside. I remember holding a Büchner sintered glass funnel and strutting across the room to the beat of the Beatles' 'Sgt Pepper's Lonely Heart Club Band' thinking, I'll show them that not only doctors and nurses wear theatre greens. Indeed, I emphasised that pharmacy demanded superior aseptic technique. Contaminate many parts of the body during surgery and body defences have a fighting chance (literally) of killing the invaders, but contaminate many sterile products (especially intrathecal) and microorganisms will multiply unimpeded.

Around 1974, at Hull Royal Infirmary, an autoclave suffered a water spray-cooling that was too coarse; inside were one hundred 1000-mL bottles of 5% dextrose infusion. One bottle exploded. A chain reaction followed: and most detonated resulting in much splintered glass..

I also advised at Hull on whether to swap from glass to the new-fangled plastic intravenous infusion packs, then a controversial issue. One patient safety concern was leaching of phthalate plasticisers. I did not then foresee that, when I became a hospital pre-registration tutor in the 1980s, I would co-operate with industry by helping to

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sign joint pre-registration graduates (six months in each of hospital and industry) onto the register of pharmaceutical chemists following experience in hospitals (Great Yarmouth and Waveney) and industry (*Travenol* now *Baxter,* Thetford). Today, large-volume infusions are seldom from glass bottles; plastic is ubiquitous.

At Whiston Hospital, Prescot in 1971 we thought nothing of sniffing or inhaling the glorious vegetable smell of bottles of Cannabis Tincture, before pouring it away, unrecorded, the afternoon before legal re-classification (Misuse of Drugs Act 1971) demanded record-keeping. Registers embossed 'Controlled Drugs' started to replace those warning 'Dangerous Drugs'.

Leeches, mainly used to remove congested blood during complex hand surgery, accidentally poured down the WC during routine cleaning of their aquarium, around 1971, were a minor hazard. Subsequently, staff sat down carefully.

A more serious potential hazard occurred at Harrogate General Hospital around 1972. If a consultant required a medicine that other consultants had recently shown was efficacious, but unavailable from industry, local hospital pharmacists were asked to manufacture it. Generally, they complied.[44] Occasionally, hypertension during some surgery was so extreme and stubborn that patients would die; commonly available hypotensives were ineffective. The heroic hypotensive of sodium nitroprusside was requested and provided. The purple analytical reagent powder was dissolved in water, aseptically transferred through a 0.2 micrometre filter into sterile glass ampoules and subsequently sealed. Needles were involved. A small volume of my concentrate was diluted in the operating theatre with 5% Dextrose injection and titrated; just drops caused a patient's blood pressure to plummet. Had I accidentally scratched myself using a needle laced with that cyanide concentrate, I would presumably have died within seconds. Moreover, the material was photolabile: whenever possible, the apparatus had to be covered with aluminium foil and the room kept dark. I remember that, rather than congratulating me on my heroism, my boss castigated me, "Get your head out of that (laminar-flow) cabinet!"

Industry

After Stockport hospitals in 1968, I decided that I would continue to manufacture but in industry and thereby earn more. Industrial salaries were lower than in retail pharmacy (subsequently renamed general practice and then community pharmacy). Institutions re-branding themselves with a new name, to distance themselves from previous perceived stigma and aiming for increased prestige, is a well-accepted sociological strategy.[45]

I became a production manager at *Calmic* Ltd, Crewe, then part of *Wellcome Foundation*, now part of *GlaxoSmithKline* plc. *Calmic's* sterile aerosol manufacturing unit was in a large hut that had been, during World War II, part of a prisoner-of-war camp. *Calmic's* offices are now a hotel.[46]

That first industrial post, mainly producing antibiotic mixtures, was under the requirement for 'adequate staff'. It was realised in the 1950s that sometimes we cannot chemically test the end product, such as insulin, sutures, vaccines or antibiotics: such production demanded extra care such as batch number records with recall procedures and 'adequate staff'. The Therapeutic Substances Act (1956; first Act 1925)[47] recognised that;[48] adequate staff included pharmacists. In time, 'adequate staff' would metamorphose into 'Qualified Persons' (QPs)[49] within the European Economic Community (EEC), later the European Union (EU). Only in 1997, when I read a history about professional chemists,[50] did I realise that political jostling for status at European and British levels, between pharmacists, chemists, biologists and others had been boiling in the 1970s, 'unknown' to rank-and-file pharmacists such as me.[51,52,53] QP certification of any batch from any country outside the EU (e.g. China, India, USA) is legally mandatory; the USA has no equivalent to the QP role.

During the *Calmic* pre-employment medical, my examiner appeared to concentrate upon my hearing and ears. I realised later that I would be handling many kilograms of finely-ground ototoxic powders. Again an accident is most memorable. I had to mix the sterile ingredients for *Polybactrin* aerosol (polymixin B sulphate, neomycin sulphate and bacitracin zinc) and then micronise, aseptically. Micronisation occurred within a sterile hammer mill. Using it, a female supervisor and I micronised within a tiny cubicle also containing a table covered with empty Kilner jars. We wore boiler suits, boots, ear protectors, hoods, gas masks, gloves and goggles.

With horror, I noticed that the mill's heavy flywheel was unscrewing. I cut the power but the wheel fell off. We jumped, simultaneously, to perch on top of the table and clung together, scattering Kilner jars. The flywheel fell to the floor and ricocheted off walls, mill and jars, splintering glass and gouging wood. The flywheel missed us. At the enquiry, I only remember being told off for damaging (expensive) company equipment.

The aseptic area was routinely fumigated with formaldehyde vapour released from its solution by potassium permanganate. The permanganate sat in jars supporting funnels, necks plugged with cotton wool to delay flow. My duty was to pour the solution into the funnels and retire immediately. Remaining would presumably have been fatal; another member monitored my progress.

We also degreased empty aerosol cans with ethanol. A tray full of cans dripping ethanol was accidentally carried over a waste bin containing incompletely-reacted potassium permanganate. Spontaneous combustion started. Contents of a large waste bin crackled, smoked and flamed like an over-sized firework. Nearby was a tank holding 100 litres of industrial methylated spirits. Moreover, just outside were two pressured cylinders each containing one tonne of *Arctons* (dichlorotetrafluoroethane and dichlorodifluoromethane) that might explode. Aiming a fire extinguisher, I extinguished the fire. Note the fluorinated hydrocarbon propellant; we knew nothing about depletion of the ozone layer. I loved swishing the

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boiling propellants about in a jug; frost ringed its edge, condensed from atmospheric water vapour. That was before concern about solvent sniffing, but we knew that, if ventilation was inadequate, asphyxiation would follow.[54]

But it was other events that made me notorious. The Laboratory Manager and I helped to develop a dry heat process to replace the chemical (formaldehyde) sterilisation of empty cans. Heat sterilisation demanded 160°C for one hour. I tried the first batch at 165°C to be certain of sterility. Unfortunately, generous can stocks were pre-painted with ink on a white background. On opening the oven door the stench of scorched paint gushed out. "I hear that you've burned the cakes," said my manager.

There was a balance between *either* heating cans sufficiently to ensure sterility but the paint becoming so discoloured that nobody would buy them *or* some cans being non-sterile but dazzling white and so favoured by purchasers. We discovered that producing cans that were both sterile and sufficiently white was possible, but only within a narrow range of conditions. We agreed the reference standard: three sterile cans on a base. One can was the whitish ideal. Another was darker but tolerable to marketing. Another was too dark. We checked every can against those standards before filling. Marketing retained an identical trio of cans.

One day a top manger blustered into my production area, "Brown! What are you doing burning my cans?" Mysteriously, on comparing the two sets of standard cans, the production set was darker than that from marketing. We realised that the set left overnight within the production area had been exposed to 'sterilising' lamps emitting ultra-violet radiation (UV). That had darkened the paint. Weeks of sorting tens of thousands of cans by shade and spraying the bottoms of the worst offenders with white (car) paint followed.

Other managers suffered disasters too. A power failure resulted in having to dig out the solidified fats for tonnes of *Drapoline* by spade. Tablet coating varnish (containing ethanol) exploded removing a tablet maker's eyebrows. But it was not all disasters. The perquisite of managers enjoying a haircut in the firm's time, fortnightly, to keep them trim, and therefore of higher status than their shop-floor workers, was welcome. I unthinkingly slotted into existing expectations for managerial appearance and taken-for-granted behaviour.

Overview

What did reflecting upon those memories teach me? Firstly, it is unfair, even cruel, for one generation to use its norms to criticise an earlier generation. That leapt out at me in connection with the aerosol propellant; we thought we were improving health. But, surveying using the 20/20 vision of hindsight, our understanding changes. We were also helping to increase both microbial resistance to antibiotics and UV radiation by reducing our planet's crucial filter, its ozone layer.

Second, I wish that I had started my writer's notebooks and other journals decades earlier in my life. Another name for a writers notebook[56] is 'commonplace book'. They have a long history from 15th century England. John Milton and Francis Bacon were famed early recorders. Universities (e.g. Harvard) have used them as reflexive aids. My note books have helped me make sense of, develop my personal 'take' on, not just pharmaceutical history, but also my life journey. Margot Asquith (1922), a UK Prime Minister's wife, said, "Keep a diary ... and later ... the diary will keep you." [57]An autobiography is a story *of* a life but memoirs are a story *from* life emphasising touchstone or turning stone events as in this pharmaceutical account. Narrators should consider the nature of their story and how best to communicate it.

Third, diary or similar entries from the specific witness are one valuable resource for historians; they report Schütz's first ('best') perspective. The Mass Observation Archive is one large-scale generalist exemplar. It specialises in material about everyday life in Britain. Source material includes the Mass Observation social research organisation (1937 to early 1950s), including diaries that ordinary people kept and newer material since 1981. The archive, parts being searchable online, is in the care of the University of Sussex.

For ethnographic sociology, medicine, pharmacy and other fields, the minimum size of a case study is just one; more is not essential. A case study may report a detail only occurring once but crucial for provoking insight. Its account capitalises upon thick rich detail[58] that carries its own stamp of credibility. History favours detail. Moreover, a personal report may volunteer conscious reasons for behaviour, important for history yet seldom divulged. This account, for example, has divulged that I left hospital for industry to earn more. The sociologist Weber gave three main reasons for behaviour.[59] Interestingly, this present discussion may provide an illustration of Weber's fourth reason that he only mentioned for completeness: affectivity. You do something because you just like it, such as having a sweet tooth, and so put sugar into your tea. Arguably, I sniffed assorted solvents more than scientific curiosity strictly dictated.

Considering pharmaceutical history specifically, only first-hand study (i.e. doing and reporting on it yourself) can show how knowledge (e.g. pharmaceutical) is ultimately transformed into practice. What professionals actually *do* may be contrary to the presumption by a lay interpreter of publicly available documents (e.g. Codes of Ethics).[60,61]

Recordings of recollections of retired British pharmacists from 1960 exist;[62] John Hunt reviewed them in 2000. Pharmacist interviews (community and hospital) exist in archives of oral pharmaceutical history, undertaken by Stuart Anderson and John Hunt. Anderson reviewed the depth and scope of oral histories. He noted they can give a more rounded picture and that the writing of autobiography is a quite common retirement pastime. He interviewed mainly retired community pharmacists (n=50); their average birth year was approximately 1920. Hunt used about 20 interviewees including retired pharmacists; their average birth year was about 1915 (range 1904-23).

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Industrial pharmacy oral history appears to be seldom reported. 'Christmas Miscellany' in the *Pharmaceutical Journal* has occasionally featured industrial pharmacist memoirs.[63,64] Histories of companies etc have featured in the *Pharmaceutical Historian*; its indexes detail about 50.

Finally, any pharmacist could offer a thick rich account of their career, but few do. Generally that eye-witness account (from Schütz's first and second perspectives) dies with her or him, and that seems a loss to successors.

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3. Schütz A. *The Phenomenology of the Social World.* Evanston: Northwestern University Press, 1967: xxvii. [Original German 1932]
4. Between generations living at the same time opinion and knowledge may differ. That affects subsequent societal memories.
5. This is simplistic. Proverbially (probably originating in the Kangxi reign period of the Qing dynasty) 'The palest ink is better than the most capricious memory'. More recently, Freud (1856-1939), for example, made us realise that memory, such as of a traumatic event, may be fallible.
6. However, that non-visual senses, such as smell, may report with at least equal certainty. In Robinson CW. *Twentieth Century Druggist.* Beverley: Galen Press, 1983: 169-170, he liked smells, such as the scent of spices, sweet smelling elixirs, syrups and emulsions and thymol.
7. For example, in UK, Cabinet Minutes are only released after 30 years.
8. 'I'. My family and circumstances also influenced my take on history. My grandfather was a hewer of coal, father a teacher. I attended grammar school, married a future pharmacist, have sons (medical practitioner, science teacher) and grandsons. In 1994 I became self-employed including industrial quality assurance auditing, internationally, until 2010.
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14. Civic prestige continues over centuries: at the Court of the University of East Anglia, Norwich, in 2014, the only luminaries identifiable by regalia or robes were three mayors wearing gold chains.
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17. Bolton P. Education Historical Statistics. *House of Commons Library.* SN/SG/4252 27 November 2012.
18. The Pharmacy and Poisons Act 1908 empowered the Society to set the 'Preliminary Scientific Examination' (PSE). The next (and final) examination was the 'Chemist and Druggist' *or* 'Pharmaceutical Chemist Qualifying Examination' (Cooper JW, Gunn C. *Tutorial Pharmacy.* London: Pitman Medical, 1950: 22.) The PSE was, by 1935, in Chemistry, Physics and Biology (Holloway SWF. *Royal Pharmaceutical Society of Great Britain 1841-1991: A Political and Social History.* London: Pharmaceutical Press, 1991: 408).
19. Pharmacy students, in their 1st year in 1964, had to pass an exam in A level Mathematics and Statistics, if they lacked A level Mathematics.
20. R. Bhundia, Royal Pharmaceutical Society, personal communication: 18 February 2015.
21. However, *University of Bradford Digest of Statistics Session 1965-66* Table 9.1 (b) Figures for registrations 1965/66 (slightly later) state about 29% female.
22. *General Pharmaceutical Council Annual Report 2012/3*: 10.
23. Binns-Hall L. University of Bradford. Personal communication: 16 February 2015.
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26. Brown ME, Ellis S, Linley PA et al. Professional values and pharmacy practice: implications for a predominantly female register of pharmaceutical chemists. *Int J Pharm Pract* 1992; 3: 178-183.
27. Brown M. Catch a good husband. *Chemist Druggist* 2000; 253: 24.
28. Opinion of fellow student: Susan Ryder (née Grainger): personal communication, 30 January 2015, also informs these figures.
29. *General Pharmaceutical Council Annual Report 2012/3:* 10.
30. Binns-Hall L. University of Bradford. Personal communication 16 February 2015.
31. Hunt J. Weights, measures, medicines and the calendar. *Pharm J* 2002; 269 (7229): 909-911.
32. Brown ME. What is a drug? *Pharm J* 2001; 267: 301-2.
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37. Brown M. A certificate's story *Pharm J* 2002; 269: 931.
38. Clarke AC. Hazards of Prophecy: The Failure of Imagination. In *Profiles of the Future: An Enquiry into the Limits of the Possible* (1962, rev. 1973), pp. 14, 21, 36. This states the third law of Arthur C Clarke: 'Any sufficiently advanced technology is indistinguishable from magic'.
39. Rifkin J. *The Zero Marginal Cost Society, The Internet of Things, the Collaborative Commons and the Eclipse of Capitalism.* New York: Palgrave Macmillan; 2004: 93.
40. Around 1980, when visiting a GP-led cottage hospital, one GP said, "So you're the … who has been scribbling all over my charts!"
The physicist Max Planck observed, "Science advances one funeral at a time" in the context that old scientists will cling onto their favourite theories, despite others changing their minds. I suggest that as old professionals die, so do their (personal) attitudes.
41. Around 1970, a very senior pharmacist observed to a meeting of pharmacists that it was easier to be served by a pharmacist than a porter. In my later experience, hospital porters were difficult to access, and those available often could not lift anything, because they had bad backs. That may be connected with lack of safety regulations and training.

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42. Wyatt HV. Personal Reflections on Investigations of Medical Crises in the 1970s; contaminated glucose drips and a smallpox case *Pharm Hist* 2015, 45 (4):83-89.

43. While at Harrogate (1971), I submitted my opinion to the DHSS on the precursor to the first *Orange Guide*.

44. A quality control pharmacist and I, for example, manufactured (Whiston, around 1971) sterile silver sulphadiazine cream before *Flamazine* was marketed.

45. Douglas M. *How institutions think.* London: Routledge Kegan, 1987: 99-101.

46. Crewe Hall, *Q Hotels* group.

47. Jepson M. From Discorides to Derrick Dunlop: developing quality standards of medicines. *Pharm Hist* 2004; 34 (1): 14.

48. Brown ME. The Quality Anthropologist. *Quasar* 2009; 106: 57-60.

49. Around 1978, the Pharmaceutical Society informed members that individuals who could provide evidence of certain industrial-type manufacturing experience in production and or quality control, and two references, could apply for inclusion in a list of persons who would have a formal role in the manufacture of medicines within the European Economic Community; details were sparse. As a District Pharmaceutical Officer in hospitals, I thought about it and decided to complete the form, just in case it might be useful one day. I completed the form and forgot it for decades. That list was of pharmacists, chemists, biologists, a few medical practitioners and others who became listed as eligible to be nominated as 'Qualified Persons'. They, by initially EEC Directive and then national laws, had to be named on manufacturing authorisations for human and veterinary products. Without their signature, no batch of medicine could be certified for release onto the market in the EU. This regulation was extended later to include investigational medicinal products (clinical trials). After redundancy from the NHS in 1994, my listing was a godsend. "You are one of *those*, aren't you?" volunteered another individual on the list, still working for the NHS. "There's money in that." Those 'grandfather' transitional regulations have long passed. Completing an MSc in industrial pharmacy has become a common academic component but is not essential. Entrance to lists of QPs is now after experience, completion of a very detailed application form, including a sponsor and oral examination. Joint examiners are from the Royal Pharmaceutical Society, Royal Society of Chemistry and the Society of Biology.

50. Russell CA, Coley NG, Roberts GK. *Chemists by profession.* Milton Keynes: Open University/ Royal Institute of Chemistry, 1977: 296.

51. Only pharmacists could be QPs in France, Belgium and Luxembourg. In the UK, Ireland, Germany and Italy, QPs could be either pharmacists or chemists. In the UK and Germany, twice as many chemists as pharmacists occupied such posts. When Britain entered the Common Market (1973) the draft directive about QPs was nearly complete and would have imposed the French system. The result would have been a monopoly for pharmacists, except that non-pharmacists already in post could continue. The Royal Institute of Chemistry (RIC) strongly opposed that pharmacist monopoly and fought through the Department of Health. The Directive should include both chemists and pharmacists. The result was a compromise. A 'competent authority' (i.e. the specific national government) should satisfy itself whether the basic qualification, such as pharmacy, chemistry or even biology, covered the specific topics (that formed most of the pharmacy course). The Pharmaceutical Society maintained that only the pharmacy degree fulfilled all. The RIC disputed it and maintained a careful watching brief to ensure that the new Directives (75/319/EEC and later, 81/851 EEC for human and veterinary medicinal products) were properly interpreted.

52. During the years 2003-5, only two, three and two pharmacists, respectively, passed the assessments to become QPs. Yet during 2003-5, 39, 24 and 24 non-pharmacists (biologists and chemists) passed. That is about twelve times more. See: Brown ME. Are pharmacist qualified persons becoming extinct? *Industrial Pharmacy* 2006; 11 (September): 18-19.

53. Brown ME. Are industrial pharmacists heading for extinction? *Pharm J* 2008; 280: 50.

54. My (inadvertent) solvent-sniffing started around 1959. Inhaling benzene, amyl acetate etc. in school chemistry laboratories was routine.

55. For example, I would be able to remember the name of that early American ward-visiting pharmacist leader.

56. Brown ME. *Winning Words A writers' helper and commonplace book to stimulate imagination.* Beccles: Watermint Publications 2014: 92-93.

57. The date of her death and my birth are identical.

58. Reeves S, Kuper A, Hodges BD, *British Medical Journal* 2008; 337: a1020doi:10.1136/ bmj.a1020.

59. Weber. M. *Wirtschaft und Gesellschaft,* 4th edn. 1956 [translated from original German 1922], Tubingen: 1, 1-14. Main reasons were self-interest, altruism and tradition.

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64. 'Christmas Miscellany' was absent in December 2014 and 2015.

Historical Evidence of Treating Vitiligo in Persia

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Vitiligo is an acquired and chronic skin disorder characterised by progressive loss of melanocytes from the epidermis and it results in depigmented areas. According to recent studies, three main hypotheses have been introduced for the pathogenesis of vitiligo: biochemical/cytotoxic; neural; and autoimmune, the latter supported by stronger data.[1] Although various therapies are practised for vitiligo, including topical and systemic corticosteroids, topical immunomodulators, photo(chemo)therapy, tissue grafting techniques and depigmentation of normally pigmented skin, these modern methods are not always satisfactory and the white patches need to be covered with colouring agents.[2] So extracting the ideas of our ancestors might both revive forgotten medicinal knowledge

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and also depict the contribution of one nation to the progress of pharmacy and medicine.

History of Vitiligo in Persia

The earliest as report of vitiligo in Persia dates back to the ancient religious text of *Avesta*. The Persian term '*paēsa*', meaning white patches, was often confused with disorders such as leprosy throughout the ages. Stigmatisation of those patients caused them to be driven out of town and to live in isolation with other sufferers. They were strictly deprived of some blessings such as ritual beverages (*hum* or milk) served by *Zarathustra* worshipers.[3] Vitiligo has also been mentioned in the documents of major religions.[4] Healing the incurable vitiligo patient (*abras*) was one of the miracles of Jesus.[5]

Ancient Persian medicinal textbooks described the etiology and treatment of vitiligo under the Persian term *pēs* or the Arabic term *baras-e abyaz*.[6] Some signs were also thought to make an accurate prognosis possible.

Etiology, prognosis and categorisation of Vitiligo

The main causes for vitiligo were thought to be dominance of humidity and/or coldness in the body, resulting in imbalance of temperament, and weakness of metabolic (*moqaiere*) power,. Under these conditions, food failed to produce normal blood that transformed into natural body parts. Scars, cauterisation and cupping sites were reported to be highly vulnerable to hypo-pigmentation and vitiligo.[7,8] Involvement of body parts near the gastrointestinal tract, such as the abdomen, was interpreted as a good prognosis, but more peripheral sites like the feet were reported to have a poor prognosis.[8] If the colour of hypopigmented patches was close to normal skin and they were not increasing in size or number, they would be the most likely curable.[9]

Two types of depigmentation disorder were mentioned in works on Traditional Iranian Medicine (TIM), including *Bahaq* and *Baras*. Moreover some indicators enabled the physician to differentiate them easily (Table 1).

Table 1. Hypopigmentation disorders and their differences according to Traditional Iranian Medicine.[8,9,10]

Indicator	*Bahaq*	*Baras*
Colour of lesions	Pale	Shiny and extremely white
Colour of lesions after rubbing	Red	White
Depth of lesions	Superficial	Deep (flesh, bone)
Exodus after pricking the skin	Blood	White moisture
Hair colour at depigmented lesions	Black or reddish brown	White
Heredity	No familial incidence	Familial incidence
Prognosis	Good (curable using topical agent)	Poor
Surface of skin	Even (no change)	Dished and softer than normal skin

Diet and treatment (pharmaceuticals and cosmeceuticals)

According to TIM's manuscripts, nutrition had an important role in causing or preventing diseases. It was considered that certain foods like dairy products, especially milk and yogurt, (salted) fish, aubergine and beef could potentially cause vitiligo and also accelerate its progress. Wet weather and excessive bathing with extremely cold water were supposed to be other underlying factors.[8,9]

Pharmaceutical treatment included some stages whose order should be followed correctly:[10]

1) Maturation of phlegm (*Enzaj*)
2) Emesis of phlegm (*Eshal*)
3) Throwing up the phlegm (*Ghai*)
4) Moderation of temperament (*Taadil*)
5) Use of topical agents (*Tela*) having a hot temperament and blood-absorbent properties
6) Systemic therapy and exposure to sunlight for certain periods
7) Colouring agents (*Sabiq*) for covering the white patches.

Table 2. Herbal- and mineral-based formulations advised for vitiligo (*Bahaq* and *Baras*).[14]

Formulation (ingredients)	Indications
Malachitis in vinegar	A mineral-based formulation recommended for both *Bahaq* and *Baras*.
Andropogon schoenanthus (flower) in olive oil or sesame oil	An herbal-based formulation advised for *Baras*
Raphanus spp. (seed extract) in sesame oil	Vitiligo
Solanum melongena (extract) *Lepidium latifolium* *Anemone* spp. *Rubia tinctorum* *Anacyclus pyrethrum* *Brassica nigra* *Helleborus niger*	An herbal multi-ingredient formulation for *Baras*, ready for use after being exposed to sunlight for 60 days. A temporary colouring agent, but use for a long time results in constant colouring of white patches
Inula helenium, vinegar, sugar and honey	An oxymel for *Bahaq*
Pistacia lentiscus, arsenic trisulphide, sulphur, asphaltum, honey and vinegar	A multi-ingredient mineral and herbal formulation prescribed for vitiligo of the nail
Pinctada margaritifera in vinegar	Advised for *Bahaq*

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It was suggested that the lesions be washed with vinegar or be exposed to steam before using topical agents.[11,12] Cauterisation was practised for small lesions.[13]

Medications were divided into simple formulations (single-ingredient) and complicated formulations (multi-ingredient) with three possible origins: herbal, mineral and animal sources (Table 2).

A unique manuscript written by *Qutb al-Din- Shirazi* about vitiligo

A special chapter on vitiligo was written in all the traditional manuscripts dealing with dermatological diseases. But a unique treatise, named *Risale fi-al-Baras* (Treatise on Vitiligo) (Figure 1), reflected the viewpoint of the famous Persian scholar *Qutb al-Din-Shirazi* (1236-1311AD) about how to distinguish and cure vitiligo.[15] Writing a specific book about this condition might show the importance of treating vitiligo, as a disease with poor prognosis, in ancient times. After introducing some therapeutic methods used by other scholars, he briefly stated the differences between *Bahaq* and *Baras*, suggested the most suitable lifestyle for such patients and presented the most highly-practised medications of that era.

Figure 1. The opening page of *Risale fi-al-Baras* (Treatise on Vitiligo) written by *Qutb al-Din-Shirazi* (1236-1311AD), National Library of Rasht.

Conclusions

Vitiligo was considered in the ancient medical texts of Persia. Two categories of this depigmentation disorder were called *Bahaq* and *Baras*. Besides the diagnostic differences of these two disorders, a variety of formulations have been suggested by Persian scholars for treating vitiligo or covering white patches. Lots of older formulations have the potential for being examined through clinical trials and developing new treatments designed according to recent standards. The effects of one traditional formulation (*sabgh*) have been compared with those of a modern marketed formulation (camouflage cosmetic) in vitiligo patients. The result of this clinical trial revealed the improved quality of life for patients in both groups.[16] Similar studies could be performed to evaluate the effect of traditional formulations and result in revival of ancient treatments.

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The impact of rabies and its treatment until the 19th Century: a lesson from the past

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Mentions of rabies are found in the early literature as far back as the 4th century BC. In the words of Aristotle, 'Dogs suffer from madness that puts them in a state of fury, and all animals which they bite when in this condition, become also attacked by madness'. This work is focused on the treatments used until the 19th century, analysing treatises that detail ancient treatments as well as more modern ones, but still based on the same ancient concepts. Current research and development are much more costly than in the past and therefore strategies for reducing the risk are sought. High-risk strategies, which explore new activity relationships, are less prevalent in the literature, reflecting a growing focus on established knowledge. We believe there is still room for investigations which start from the re-investigation of ancient recipes in the light of the latest technologies and equipment.

Introduction

Rabies is an infectious disease. The rabies virus is a species of the *Lyssavirus* genus, in the family *Rhabdoviridae*, order *Mononegavirales*. The word 'rabies' originates from the Latin *rabere* to rage or rave. Before Pasteur's discovery of a rabies vaccine, patients were shocked and afraid of a possible development of the disease leading to death. Alongside stories about werewolves and vampires, there was only one absolute certainty: survival was almost impossible. References to rabies are found in the early literature as far back as the 4th century BC. In the words of Aristotle, 'Dogs suffer from madness that puts them in a state of fury, and all animals which they bite when in this condition, become also attacked by madness'. References to the disease are found in the works of Virgil, Horace, Ovid and Plutarch. In humans, the disease was first recorded by Celsus in the 1st century AD, and he applied the name 'hydrophobia'. Galen, in the 2nd century AD, prescribed special remedies for rabies.

The transmission of the disease to humans by rabid wolves was recorded in 1591. An epizootic of rabies appeared in Paris in 1604, toward the end of the 17th century in Italy, and during the 18th century in France, Germany and England, and was first reported in the United States in 1768. Toward the end of the 18th century and during the 19th century, rabies had spread all over Europe. In Australia, it has been kept out by the enforcement of rigid quarantine laws. In the United States and throughout North America, the disease is widely distributed. Between the years 1876 and 1882, 44 people died of rabies in Massachusetts, then 45 deaths were recorded from 1888 to 1894,. From 1895 to 1908, according to Massachusetts Health Board statistics, 497 people were exposed to rabies and were given the Pasteur treatment.

Aim of the research and sources

This work is focused on the treatments used until the 19th century. In the first document,[1] *Discorsi di Dioscoride*, Pietro Andrea Mattioli reported and analysed the text of Dioscorides, resulting in an overview of ancient and contemporary (16th century) knowledge (Figure 1).

Figure 1. *De i segni del cane rabbioso*. I Discorsi di M. Pietro And. Matthioli sanese. In Venetia: Appresso Vincenzo Valgrisi MDLIX.[1]

Other 18th and 19th century rabies treatises[1-28] have been analysed. In the last considered essays, Luigi Toffoli, member of the *Accademia medico-chirurgica di Ferrara,* still linked rabies to ancient theories.[5-26] Our efforts in the field of the History of Medicine and Pharmacy are addressed not only to raising the profile of the History of Medicine and Pharmacy within the scientific community, but also to disclosing the field to the general population as a part of the traditional knowledge that needs to be preserved from globalisation. Furthermore, the History of Medicine and Pharmacy plays an important role in supporting modern pharmaceutical science and clinical practice today, as demonstrated by the link to current researches. Some examples of this will be reported throughout the present work.

Rabies treatments as reported by Pietro Andrea Mattioli in *Discorsi di Dioscoride*

He considered the human body consists of four cardinal humours: blood coming from the heart; phlegm from the brain and expanding to the whole body; yellow bile secreted by the liver; and black bile going from the spleen to the stomach. These four humours circulate in our body and, when combined in various ways, lead to health or disease. Sometimes they are too abundant, sometimes insufficient. They often decay, putrefy and are corrupted, and illness appears. Expelling these corrupted humours is the task of a drug, which will act differently in relation to its qualities and structure. Purgatives, emetics, diuretics and diaphoretics are among the favourite medications. Stress conditions, such as extreme cold or heat, lead to an imbalance of humours by causing a consequential illness.

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Dogs become 'melancholy', and rabid. Infected humans become melancholy as well. Symptoms of rabies were anxiety, confusion, agitation and hallucinations. Patients became dangerous to themselves and others. Dogs either became ill by eating animals that died from the bite of poisonous animals, or because of lightning, or also by drinking cloudy and putrid water. In Galen's opinion, dogs were not the only animals to become rabid. It was also possible for foxes, wolves, weasels, martens, baboons and many others. Aristotle in the *VIII libro della Historia degli animali* also included camels and horses, and Avicenna also included mules. The dilemma was: were these last cited animals rabid because of a bite?

Treatments for rabies were the usual remedies used for the bite of venomous animals and there were also specific remedies for the bite of a rabid dog. Freshwater crabs burned with shoots and crushed gentian roots were mixed with wine to obtain a paste which was administered by mouth. If late, the dose was tripled. Crab powder was known as a rabies remedy and gentian as an alexipharmic. Some physicians confused freshwater crab with crayfish (Fig. 2). Crabs were called *Molleche* in Venice.

Scratches were worse than wounds as they could not expel the poison by bleeding. Torn parts had to be cut out with a razor. The venom had to come out of the body. Suction cups were employed in this process, and the addition of incense could increase its efficacy. A plaster made of tar, strong vinegar and opoponax was employed. Opoponax is a gum resin said to be obtained from the *Pastinaca opoponax* tree by a trunk or root incision.

Incense was replaceable with turpentine. Alyssum in honeydew water could be administered and treatment continued for 40 days. Jewish bitumen (*Bitume giudai)*, recommended by Aetius and administered with water treated patients with the fear of water. Seahorse (*Hippocampi marini*), minced with black vinegar and honey, could be drunk or applied to the wound.

A decoction of *Rumex* sp. L. (*romice* or *lapazio acuto*), was used to wash wounds after grass was applied to them. It is interesting to note that in a recent paper the dimeric proanthocyanidin epicatechin-3-O-gallate-(4ß-8)-epicathechin-3'-O-gallate (procyanidin B2-di-gallate) was identified as the main active principle of *Rumex* and that an enriched extract protects cells from influenza virus infection (an RNA virus like rabies) by inhibiting viral entry into the host cell. *R. acetosa* and procyanidin B2-di-gallate appear to be a promising expansion of the currently available anti-influenza agents.[29] The powder was drunk to purge the urine. The same key ingredient was also found responsible for inhibition of HIV virus replication (another RNA virus).[30]

Avicenna suggested cantharides, with blood in the urine as a sign of healing. Galen recommended oral or applied theriac. Common remedies were pondweed (*Potamogeton* spp.) plastered with salt on the bite, bark of wild fig pounded and drunk with water), wormwood, garlic, centaury, aristolochia, artemisia, germander (*Teucrium, camedrio*), water germander (*Teucrium scordium,* an alexipharmic or antidote to poison), bryony roots, pennyroyal, and *Silphium* (*lasero,* taken orally or applied to the wound*)*. In a recent research project that aimed to investigate natural products in drug discovery, the *in vitro* cytotoxicity and antiviral activity of extracts from traditionally used Mediterranean plants were highlighted as effective inhibitors of the replication of several viruses. This is another confirmation that ancient recipes were weak remedies in their traditional use but were not devoid of rational observations.[31] As an example, the literature contains several reports of the antiviral activity of *Artemisia*.[32]

Roasted liver of rabid dog was a more imaginative remedy, but Dioscorides disagreed with this method and Galen was doubtful about it. Dioscorides said that a tusk of a rabid dog could be tied to the arm in a leather bag in order to free patients from the fear of the water.

It was necessary to release the blood with razors, suckers or leeches. Bloodletting was not recommended as it could draw the poison inside. Or you could rely on St Donino and St Bellino: certain priests performed exorcisms and administered the so-called Benedict bread, which they may have thought contained something like a medicine. A safe treatment was cautery: fire would defeat the poison for sure. The wound should be kept open with salty things, with chopped wild garlic, onions and Cyrenaic liquor (*Medico Parthico*).

Wheat seed (both whole and wheat chewed while fasting) was applied to the wound. This could permit healing by increasing its volume and by expanding the wound continuously. It should be open, cut and cauterised, then a poultice made of salts should be applied followed by crushed mustard. Poultice, adhesive plasters, pitch, turpentine, and gum were recommended. The wound had to remain open for 40 days.

Rabies treatments reported in treatises of the 18th and 19th century

Mercury was ubiquitous in medical practice, especially in the 19th century, and was also used in the treatment of


De i Granchi de i fiumi. Cap: X.

LA CENERE de i Granchi de i fiumi bruſciati, data tre'dì à bere alla quantità di due cucchiari insieme con un cucchiaro di radice di gentiana, gioua efficacemente al morſo del cane rabbioſo. Impaſtata con mele cotto, mitiga le fiſſure del ſedere, & de i piedi, le bugance, & i cancari. Triti, & bevuti crudi con latte di aſina, giouano al morſo de i ſerpenti, de i ragni, che chiamano phalangi, & alle punture de gli ſcorpioni. Cotti, & mangiati con la loro decottione, giouano, à i phtiſici, & à chi ha neſſe beuuto il ſepre marino. Meſsi triti cõ baſilico ſopra à gli ſcorpioni, gli ammazzano. Tutto queſto ſanne anchora i marini, ma con aſſai minore ſucceſſo.

SONO in manifeſto errore coloro, che ſi penſano, che i Granchi ſcritti da Dioſcoride, & da Galeno, ſieno quelli che volgarmente per tutta Italia ſi dimandano Gambari. Imperoche carcinos in Greco (come ſcriue Dioſcoride nello eſtratto) ſignifica il granchio marino, quale chiamano i Greci aſtacos: ma quello di ritõda figura, et ſenza code

Nel ſecondo lib. di Dioſcoride. 195

che noi chiamiamo propriamente in Toſcana Granchio: & à Vinegia, doue ne viene de marini una infinità, quando hanno mutato il guſcio ſi chiamano Molleche, della cui ſpetie ſono anchora quelli che chiamano Macinette, ſe

Figure 2. *De I Granchi de I fiumi*. I Discorsi di M. Pietro And. Matthioli sanese. In Venetia: Appresso Vincenzo Valgrisi MDLIX.[1]

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rabies. Ravelly was the first to propose the use of mercurial preparations against rabies in *Traité de la maladie de la rage* in 1696.[2] The use was internal, as morsels. Later, mercurial frictions were also proposed. The aim was to cause salivation.

(a) Non immediatamente, ma più preſto. Anzi ſonvi non poche oſſervazioni di ferite anche gravi alla faccia, le quali non furono ſeguite da *idrofobia*. Vedaſene una notabiliſſima nel RAVELLY (*Traité de la maladie de la rage. Metz* 1696. 12.). Queſto Medico è ſtato peravventura il primo a proporre contro la *rabbia* l'uſo interno delle *preparazioni mercuriali*: ecco le ſue ricette:

℞. *Antimon. diaphoretic. g. xx,*
cinnabar. antimon. g. x,
ſal. volatil. e cornu cervi g. xii,
camphor. g. v; m. f. b.

Oppure

℞. *Mercur. dulc. g. xii, vel xv,*
pulver. oculor. cancror. præparat. g. xij,
ſal. volatil. e ſuccin g. v;
cum conſerv. roſar. ſ. q. miſ., f. b.

L'uno, o l'altro di queſti bocconi ſi dee prendere ogni mattina a digiuno, purgando il malato ogni

Figure 3. Ravelly preparations against rabies.[3]

In the third edition (1787) of an anatomical-surgical treatise of 1759,[3] mentioning Ravelly, all treatments of the time were traced: use of caustics; mercurials for internal and external use, turbit, powdered oyster shell alone or with herbs, meadowsweet, *Polypodium* fern (from near oaks), centaury; wormwood, St John's Wort, plantain, rue; betony, artemisia, lemon balm, savin, vervain, mint (powder of *Palmario*), leaves of rue, garlic, filings of tin, wine (Remedy of *Mayerne*), powder of terrestrial lichen, cinnabar (mercury sulphide) and mosses, opioids and antispasmodics, immersion and submersion, strong purgatives and hellebore (Dioscorides), and cantharides (Rhazes). The use of drastic purgatives and overly abundant bloodletting was not approved. Other remedies, like the most innocent powder of *Palmario* or the powder of oysters, were provided to please the patient, while continuing with other more effective remedies. Further remedies, such as pimpernel, *angolam* (a Malabar tree), scarabs and belladonna, are cited.

Rabies and its treatments were the subject of study both for physicians and for veterinarians. Scarlet pimpernel (*Anagallis arvensis*) was investigated in one single study and found active; the action was due to inhibition of virus-host cell attachment. In particular, the main component, a saponin, interfered with both early and late stages of herpes virus replication.[33]

A passage in a veterinary treatise edited by Hurtrel D'Arboval is very interesting.[4] Beside the usual prescriptions, bloodletting, emetics, purgatives, and, of course, antispasmodics, unexpected and prolonged diving in the sea or in fresh water were recommended. Other remedies included: oyster shell powder, mercury, artemisia, wormwood, white hellebore, cantharides, onion, root of plantain, opium and chlorine. Drinks or mucilaginous mash, infusions with orange leaves, arsenic, *scordio* (*Teucrium scordium*), sabine, clove, liverwort, wild valerian, *Scutellaria laterifolia*, copper filings, and tin filings mixed with theriac or Mithridate were suggested as remedies. The use of tin filings against the bites of rabid dogs was very well known. Cantharides beetles, *Lytta vescicatoria*, are well known for their vesicant properties due to an irritant component, cantharidin, a terpenoid comprising up to 5% in the insect. It is interesting to note that cantharidin has proved inhibitory activity against HBV virus in comparison with lamivudine and ribavirin.[34,35] Most of the activity of *Scutellaria laterifolia* is certainly due to its high flavonoids content (baicalin and its aglycone baicalein). The related plant *S. baicalensis*,[36] in view of the content of baicalin, has been shown to inhibit a number of viruses including Epstein-Barr[37] and influenza[38]. The flavonoids have demonstrated strong inhibition of reverse transcriptase and *in-vitro* inhibition of HIV infection[39].

As mentioned in the literature, pimpernel (alone or with ammonium carbonate), terrestrial lichen *cerognolo* (*Lichene cerognolo terrestre*) and *Meloe proscarabaeus* beetle were suggested as remedies against the bites of rabid dogs. *Anagallis* (pimpernel) is a plant of *Ranunculaceae.* Some species are still used in medicine. The decoction of this plant was used for plagues and bites of vipers and rabid dogs, while the juice was used for the treatment of scurvy. The use of the powder and extracts was reported in the Campana's *Farmacopea ferrarese* against hydrophobia.[40] *Lichene cerognolo terrestre* is an organism resulting from the symbiotic association of a fungus and an alga. Its use as a remedy against the bite of rabid dogs was just a popular belief as its effectiveness had never been demonstrated. *Meloe proscarabaeus* is reported in Campana: *Meloe majalis Lin. Meloe proscarabeus Lin Insetto intiero.* These insects were the ingredients of the electuary against rabies that was published in Berlin a few years before. Their supposed therapeutic activity is nowadays ascribed to the content of cantharidin (in particular in *majalis*) for its vesicant and diuretic properties.[41]

Tobacco, *Asclepias*, root of *Corydalis ussuriensis* (*aparina*), ash bark, and camphor (known as an antidote for the stings and bites of poisonous animals) were also reported as remedies. Tobacco is a herbaceous plant of *Solanaceae*. The juice was used for stings and bites of poisonous animals. To support the traditional use, a recent study has described the antimicrobial activity of cembranoids from tobacco leaves.[42]

Asclepias, milkweed, is a shrub of the Gentianaceae. The powdered root was considered a good antidote for bites of poisonous animals. Juice of *aparina* that was purified, mixed and drunk with warm white wine was used against the bites of poisonous animals. Ash is a tree of Oleaceae; Dioscorides advised applying the juice from its leaves to the wounds caused by snakebites. Camphor also acts as an antidote against bites of snakes.

Pimpinella, garlic, sage, pepper and vinegar remedies were known as alexipharmics (antidotes), as reported in this veterinary treatise. *Pimpinella* (also known as anise) is a herbaceous plant of the Umbelliferae. Boiled garlic root was used against intestinal worms and, if boiled in milk, it was a very powerful alexipharmic. Beside this, a

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very recent publication has confirmed the use of this herb in infective diseases.[43]

Salvia (Labiatae) as a decoction was effective in spasmodic contractions, such as epilepsy. It was also considered an alexipharmic. The water produced by the distillation of the flowers was prescribed to prevent the poisons. *Pepe lungo*, pepper and vinegar were known as alexipharmics.

Belladonna, asafoetida, meadowsweet and mint, which were commonly used as antispasmodics, were suggested for the treatment of rabies. Belladonna is a herbaceous perennial plant of the *Solanaceae* from which atropine was extracted and used medicinally as both an analgesic and an antispasmodic. Asafoetida gum resin derives from the root of a native Persian plant, and was used as an antispasmodic. Meadowsweet (Rosaceae, *ulmaria*)) is used as both an antispasmodic and antiepileptic. Mint (Labiatae) was used as a balsamic oil for the treatment of convulsions. Some of these plants, in view of their traditional uses, have been re-investigated in recent years.[44,45]

Sleep apple (bedeguare) is an outgrowth that forms on branches and fruits of *Rosa canina,* and from which tannin was extracted. The outgrowth appears at the point where the gall wasp *Cynips* attacked the plant.

In Campana's *Farmacopea ferrarese*,[40] the decoction of broom *Spartium scoparium, ginestra*) was proposed as a treatment for hydrophobia as a gargle, in addition to the remedies mentioned above.

Existing blisters under the tongue, near the frenulum, were freed from the poisoned hydrophobic matter first. After that, they were cauterised and the patient had to gargle. The same decoction had to be to drunk for six weeks after the operation described.

All these remedies were confirmed by Ederle:[27] prophylactic measures, local applications to the wound (with a view of preventing the absorption of the hydrophobic virus), amputation, cautery, cupping-glasses and *Belladonna*, *Anagallis arvensis*, *Lichen cinereus* (principal ingredient in *pulvis antilyssus* of Dampiere), water plantain (*Alisma plantago*), *Scutellaria lateriflora*, strong vinegar, cantharides, *meloe majalis*, and opium. No remedy could be considered better than mercury to prevent hydrophobia.

Luigi Toffoli

Luigi Toffoli (1796-1867) was a chemist-pharmacist who published a myriad of treatises on rabies. Among many societies, he was a member of the *Società Medico-Chirurgica* of Ferrara. Many of his volumes are present in the library of this academy,[6-25] while only one can be found in the University library[26]. In three of his works – two[17,18] in 1859 and one[25] in 1864 – his theories are clearly expressed: *Rabbia primitive* (primitive rabies) is developed in the dog, and then transmitted to other animals and humans. A health plan for animals was useful to prevent rabies through the segregation of dogs. Conflicts with rivals and sexual frustrations could be avoided for possible development of the primitive rabies in the dog. In the treatise *Sulla rabbia ed altri argomenti: lettera al dott. Luigi Bosi* [On Rabies and other arguments: letter to Dr Luigi Bosi],[24] which was published in 1863, we can find a clear link to the *Accademia di Ferrara* (the letter is addressed to Bosi, ex-President of the same). In some works, acclaim from eminent colleagues emerges. These baseless theories apart, what is reported in *Osservazioni di Luigi Toffoli sopra il rimedio contro l'idrofobia pubblicato d'ordine superiore in Parigi* [Observations of Luigi Toffoli on the remedy against hydrophobia published by the higher order in Paris] (1836) are very useful for our research to continue describing the remedies of the 18th century.[5] Toffoli did not approve of washing the wound with a rough diaper and squeezing the blood to irritate the skin. Even the use of cupping was judged not very reliable. In contrast, he approved: showers; making wounds more extensive (as stated by Aetius) to release as much blood as possible; washing with chlorine solution; and cauterising deeply and widely with caustic, with application of plaster vesicant in order to maintain an abundant suppuration. He agreed with Celsus, Aetius and Dioscorides regarding the use of surgical instruments. He suggested either the amputation of 'part-biting' (in the case of fingers, hands and feet) as a safe remedy, or the cauterisation (*ambustione*) with a red-hot iron when the wound is wide but not deep. Cauterisation with *butirro di antimonio*, the use of oil of vitriol and silver nitrate powder methods are abandoned. The preparation *Butiro di antimonio* (antimony chloride) is reported in the *Farmacopea ferrarese* of Campana.[40] The caustic product had an oleaginous consistency, which is why it was called *butirro* (butter).

Francesco Jachetti, professor of the School of Pharmacy in Ferrara, was also a member of the *Accademia* and wrote on hydrophobia.[28] Remedies were: cauterisation (chlorine or fire), *Parenti* powder (made of cantharides and pepper), enemas (made of antispasmodics or of *Nicotiana*), epigastrics, morphine acetate pills, opium, calomel, and finally, blessing with the keys of St Donino. Symptoms of rabies were vesicles under the tongue, as described by Marocchetti.

At the end of the 19th century, the research of Pasteur led to the discovery of the agent responsible for the disease. It had a neurotropic character and it was demonstrated that the virus was present not only in saliva, but also in the nervous system. In 1884, Pasteur produced the attenuated virus, which allowed him to develop a vaccine in 1885. In that year, the vaccine was used for the first time to treat a child in an emergency situation. This child, Joseph Meister, remained at the Pasteur Institute as a collaborator.

Louis Pasteur

On Monday 6th July 1885, Joseph Meister, aged nine, was brought by his mother to Pasteur from Alsace in the hope of preventing the disease (Figure 4). He had been bitten by a rabid dog on 4th July Several factors made Pasteur's potential involvement in the boy's care controversial.

Pasteur had never before successfully used the vaccine on a human. Pasteur's notebooks indicated that two previous attempts had been made. One involved a 60-year-old man who left the hospital after only one injection and did not return. The other was a 10-year-old girl, treated with one injection, who died before the second could be given.

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The concept of attenuation of viruses and bacteria was at an embryonic stage at this time. Injecting a human with a disease agent, even a weakened one, was a new and controversial action. Pasteur was not a medical doctor and might have faced serious consequences had Meister not survived the injections. Louis Pasteur felt certain that the boy would die from rabies infection if he did nothing. With some reluctance, the scientist was persuaded by Drs Vulpian and Grancher of the Académie de Médecine to give Dr Grancher the emulsion from the cord of a rabbit that had died of rabies on 21st June, and had been kept in dry air for 15 days.[46-48] The child was given 13 further inoculations over 10 days with portions of the rabbit spinal cord that were progressively dissected so as to enable the attenuation of the virus in order to become avirulent. The vaccine was thus produced. After three months and three days he announced that the child's life was now out of danger and his health appeared excellent. Meister never developed rabies, and the incident was regarded as a success. Later in life, Meister became the protégé of the chemist, who made him guardian of his Institute and then, after the scientist's death, he became the guardian of Pasteur's tomb at the Institut Pasteur in Paris.[49] On 20th October of the same year, Pasteur successfully treated another patient infected by a mad dog six days earlier. By 1886, he had treated 350 patients from all over Europe, Russia and America.[50-51]

The death of Joseph Meister

From at least 1950 a mythical version of his death circulated widely. It was said that inn 1940, during the German occupation of France, Joseph Meister, the first man in the world that Pasteur had vaccinated and saved from rabies, now aged 64 and caretaker of the Pasteur Institute in Paris, refused to allow Wehrmacht officers who asked to visit the crypt of Louis Pasteur to enter the tomb in which the scientist and his wife since had rested for 45 years. Unable to prevent the soldiers from entering, Meister was said to have returned home to 25 rue du Docteur Roux, where the famous Institute is located, and committed suicide with his service revolver, which he had held since the First World War. The history of the dispute with the German soldiers was not however supported by additional elements or definitive evidence. But there is also another hypothesis that would seem the most accepted suggesting that Joseph Meister did not shoot himself with his revolver from the 1914-18 war, but committed suicide with gas.[52] On June 13, while the Germans were approaching Paris, Joseph Meister had forced his wife and two daughters to leave Paris against their will. About ten days after the capitulation of France, Meister, having no news of them, was persuaded of their death. Judging himself guilty, he wanted to end his days by committing suicide in his house with a gas stove, on June 24, 1940. That same evening, however, Mrs Meister and her daughters returned to the Pasteur Institute and learned of his death. Eugene Wollman wrote in his diary:

> If Meister had resisted for 24 hours to his trouble and depression for his family, everything would be back to normal.[53]

Contemporary sources and family narration from his grand-daughter, Marie-José Demouron did not mention an incident with the Wehrmacht. At the time of his suicide, representatives of the German army came several times to the Pasteur Institute, which became the centre of medical reference for venereal diseases for the occupying troops.

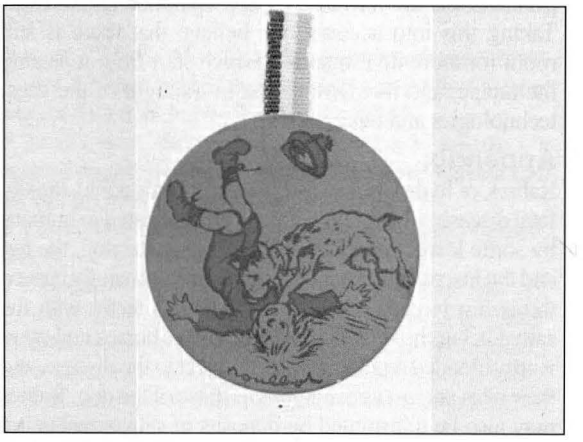

Figure 4. A 1923 commemorative tag represents the attack on Joseph Meister, the first person on whom Pasteur successfully used rabies vaccine. *The Historical Medical Library of The College of Physicians of Philadelphia.*

Conclusions

The four cardinal humours theory, which identifies the disease as an imbalance in the temperaments, defines the rabid melancholy. The theory that rabies could arise spontaneously in animals in stress conditions persisted until the 19th century (Toffoli). Transmission through the dog bite and saliva was known. The reliable solution, amongst many proposals, was either the use of a red-hot iron or amputation. The use of the razor to remove open parts that may have come in contact with the saliva and keeping the wound open for at least 40 days in various ways could not guarantee a cure. Scratches are more dangerous because they do not bleed. The wound should be washed and left to bleed as much as possible. Cupping glasses can be used. Bloodletting must be avoided as it would attract the evil in the body. The main remedies are classic alexipharmic treatments. Mercurial compounds are also used for internal use and as frictions. In the late 19th century, thanks to Pasteur, the vaccine finally arrived.

Current research and development are much costlier than in the past and therefore strategies for reducing the risk are sought. High-risk strategies, which explore new activity relationships, are less prevalent in the literature, reflecting a growing focus on established knowledge at the expense of new opportunities.[54]

In this context, an approach that takes into consideration past experience, such as those deriving from tradition, can be less expensive in terms of costs and time, thus reducing overall investment. Descriptions of traditional remedies are very useful in this contest,

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because traditional uses still represent the largest 'clinical' study ever conducted by human beings.

One of the most complex aspects in reviewing ancient preparations is, however, related to the Galenic, i.e. preparative methodologies, which are not easily understandable and do not make clear what part of the activity is linked to original molecules or their by-products that are formed during preparation and storage. Taking this into account, we believe that there is still room for more investigations which start from repeating the recipe, and its investigation in the light of the latest technologies and equipment.

Appendix

Rabies, or hydrophobia, is a specific, highly acute, rapidly fatal disease, which is generally communicated to humans by some lower animal, most commonly the dog, the fox and the insect-eating bat. The infection is generally carried through a wound made by the animal's teeth, with the saliva being the infective medium. Cats, horses and other warm-blooded animals are also subject to the disease, and their bites are just as dangerous as those of the dog. Rabies may also be transmitted by deposits of saliva containing the virus on abraded surfaces, such as by licking, or through wounds received while performing autopsies on infected subjects. The saliva of the dog has been shown to be virulent 24 to 48 hours before the animal exhibits any symptoms of illness.

The disease in the dog appears in two forms: the dumb variety, which is by far the most common, and the furious type, which because of its wild, migratory character is more dangerous to the community. The dumb variety is characterised by progressive paralysis of the lower jaw and marked nervousness, and death usually results within three to six days. The animal may appear very affectionate, but may bite without warning. In the furious type, the dog will bite anything which comes its way.

The incubation period varies with the severity and location of the bite, the virulence of the virus, and the species of the animal that is biting and is being bitten. In humans, the incubation is roughly from 14 to 90 days or longer; in dogs, 14 to 60 days, but it may be as short as 6 days; in rabbits, 9 to 90 days; in guinea pigs 8 to 60 days. After the central nervous system infection is established, the virus spreads by autonomic and sensory nerves to multiple organs, including the salivary glands of rabies vectors including dogs and secreted in saliva.

The Pasteur treatment has reduced the mortality from rabies from about 16% in the untreated, to 1% or less, in the treated. Its effectiveness depends upon the incubation period being sufficiently long for an immunity to be established before the onset of the symptoms. Failure may be due to the virulence of the infection, proximity of the wound to the nerve centres, or a delay in the administration of the treatment.

The treatment is described as 'an emulsion of the cords of rabbits that have died as a result of the subdural injection of fixed rabies virus'. The fixed virus is obtained by passage of the rabies virus through a long series of rabbits until the animals die after a uniform period of incubation; this period may vary according to the strain of virus. The cords are removed from the rabbits and, as a rule, dried over potassium hydroxide for a period of from two to fifteen days. Antirabies vaccine is used for the preventive treatment of rabies.

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avvertenze importantissime che si devono avere nelle famiglie ove si tengono cani, per impedire il primitivo sviluppo della rabbia; cautele da osservarsi durante gli amori canini, da cui principalmente dipende la salvezza della società: breve istruzione popolare. Padova: GB Randi, 1859.

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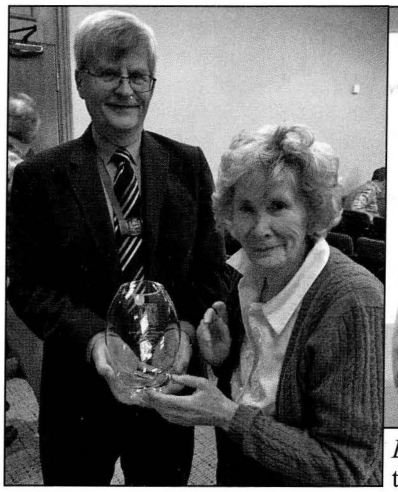
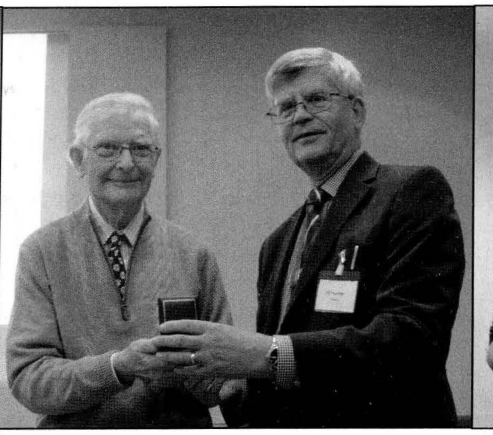
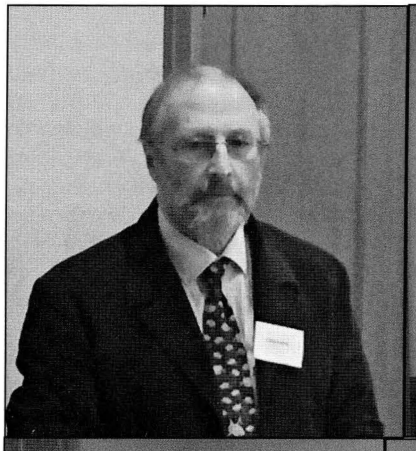
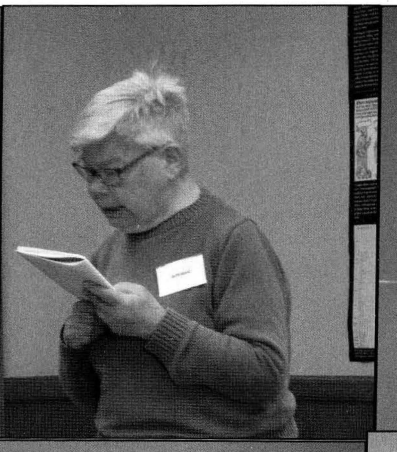


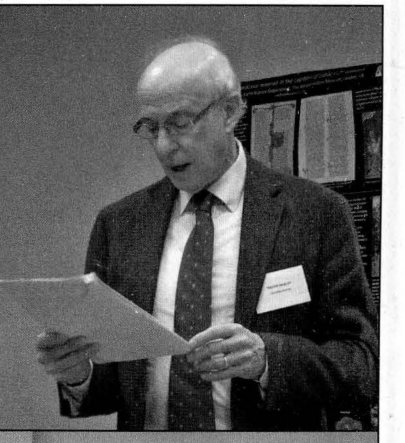


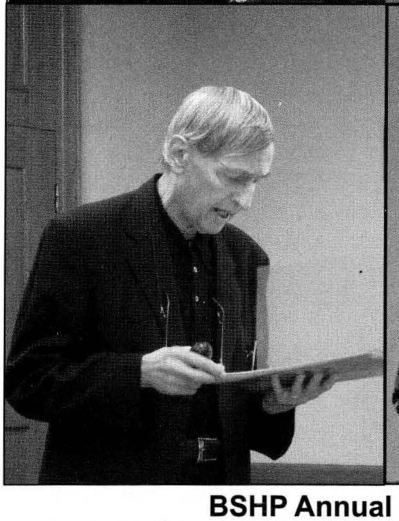
Photos: Peter Homan and Christiane Staiger

Left to right: Presentation by Roy Allcorn to Ann Hutton, who served on the BSHP Committee for more than 40 years; Presentation of the Leslie Matthews Medal to Dr John A Crellin; Anastasia Schulze, Winner of the Burnby Award 2016 giving her presentation on 'The Benzodiazepine Crisis 1960 to 1990'.









BSHP Annual Spring Conference, Reading, March 2016

Speakers at the Conference, *clockwise from upper left*: Dr Chris Duffin; Ruth Segal; Trevor Whaley; Dr Christiane Staiger; Dr John Crellin; Renzo Console.

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